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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,594	06/22/2000	Irina Nazarenko	0942.4980002/RWE/SEZ	8750
7590	08/12/2005		EXAMINER	
Sterne Kessler Goldstein & Fox PLLC Suite 600 1100 New York Avenue NW Washington, DC 20005			FREDMAN, JEFFREY NORMAN	
			ART UNIT	PAPER NUMBER
			1637	

DATE MAILED: 08/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/599,594	NAZARENKO ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 18 July 2005.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 10-15,17-22,47,59,63-67 and 76-80 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 10-15,17-22,47,59,63-67 and 76-80 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|  | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 18, 2005 has been entered.

***Status***

2. Claims 10-15, 17-22, 47, 59, 63-67 and 76-80 are pending.  
Claims 10-15, 17-22, 47, 59, 63-67 and 76-80 are rejected.
3. Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable. In particular, the new language which requires that there is a single type of detectable label having the same chemical structure overcomes the Tyagi and Nazarenko references since these references require the use of labels with different chemical structures. Even if fluorescein and rhodamine, for example, are both the fluorescent labels and therefore the oligonucleotides labeled with both of them have only a single type of label, a fluorescent label, these labels do not have the same chemical structure. Therefore, since Tyagi and Nazarenko require the use of labels with different chemical structures, these references no longer anticipate the claimed invention.

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 10-15, 17-20, 47, 59, 66, 67, 80 and 83 are rejected under 35 U.S.C. 102(e) as being anticipated by Horn et al (U.S. Patent 6,465,175).

Horn teaches a method of claims 10, 20, 47 for quantification of target nucleic acid molecules in a sample comprising hybridizing labeled oligonucleotides with the target molecules and quantifying the amount of the target nucleic acid molecules (see column 3, lines 7-20),

Wherein said one or more oligonucleotides are labeled with only a single type of detectable label, said single type of detectable label having the same chemical structure (see column 3, lines 7-20, where only a single label is used)

And said one or more labels undergo a detectable change in an observable property upon said hybridizing (see column 3, lines 7-20, where the label is fluorescent when the probe is single stranded by is quenched when hybridized).

In particular, Horn shows in example 1 at columns 13 and 14, that the BODIPY FL label was capable of being quenched by hybridization when it was directly linked to the probe, but not when it was linked via a linker which rendered it distant from the

hybridization. In example 3 at columns 15 and 16 and in figure 1, Horn shows quenching with multiple labels with the same chemical structure, that of BODIPY FL. Horn makes the use of a single label explicit in example 5, where a modified Taqman assay is taught in which an oligonucleotide singly labeled with BODIPY FL is used without the use of a quencher dye (see column 17, lines 50-55).

With regard to claims 11, 12, Horn further teaches combining the method with nucleic acid amplification assays (see column 2, lines 50-55).

With regard to claims 13, 80, 83, Horn teaches the use of BODIPY FL, a fluorescent label (see column 10, lines 30-65, for example).

With regard to claims 14, 15, Horn teaches measurement of the fluorescence during PCR (see column 17, example 5), during LCR (see example 7, column 18) and during SDA (see example 9, column 19).

With regard to claims 17, 19, 59, Horn teaches the use of hairpin oligonucleotides (see figure 4, panel B, for example).

With regard to claim 18, Horn teaches application of the method to PCR (see column 2, line 55, for example).

With regard to claims 66, 67, Horn teaches placing the dye at the 3' termini (see column 13, line 39).

#### ***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horn et al (U.S. Patent 6,465,175).

Horn teaches a method of claims 10, 20, 47 for quantification of target nucleic acid molecules in a sample comprising hybridizing labeled oligonucleotides with the target molecules and quantifying the amount of the target nucleic acid molecules (see column 3, lines 7-20),

Wherein said one or more oligonucleotides are labeled with only a single type of detectable label, said single type of detectable label having the same chemical structure (see column 3, lines 7-20, where only a single label is used)

And said one or more labels undergo a detectable change in an observable property upon said hybridizing (see column 3, lines 7-20, where the label is fluorescent when the probe is single stranded by is quenched when hybridized).

In particular, Horn shows in example 1 at columns 13 and 14, that the BODIPY FL label was capable of being quenched by hybridization when it was directly linked to the probe, but not when it was linked via a linker which rendered it distant from the hybridization. In example 3 at columns 15 and 16 and in figure 1, Horn shows quenching with multiple labels with the same chemical structure, that of BODIPY FL. Horn makes the use of a single label explicit in example 5, where a modified Taqman assay is taught in which an oligonucleotide singly labeled with BODIPY FL is used without the use of a quencher dye (see column 17, lines 50-55).

With regard to claims 11, 12, Horn further teaches combining the method with nucleic acid amplification assays (see column 2, lines 50-55).

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With regard to claim 18, Horn teaches application of the method to PCR (see column 2, line 55, for example).

With regard to claims 66, 67, Horn teaches placing the dye at the 3' termini (see column 13, line 39).

Horn does not teach each possible location of the internal base.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to adjust the exact positioning of the bases near the 3' end, since the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

#### ***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 10-15, 17-22, 47, 59, 63-67 and 76-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of the fluorophore BODIPY, does not reasonably provide enablement for the use of other fluorophores such as fluorescein or rhodamine and provides no discussion on the use of non fluorescent labels. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

#### The nature of the invention

The claims are drawn to a method of nucleic acid quantification with a single detectable label (with a single chemical structure). The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

#### The breadth of the claims

The claims encompass a method of nucleic acid quantification with a single detectable label (with a single chemical structure). The method broadly encompasses the use of the method with any label whatsoever, including any fluorescent label, any chemiluminescent label and any other type of label including haptens or other markers. Thus, the method encompasses everything from the use of small molecules such as

BODIPY or fluorescein to the use of large macromolecules such as proteins or antibodies as labels.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the ability of a label, bound to a nucleic acid, to undergo a detectable change upon hybridization of that nucleic acid. Identification of such labels is an inventive, unpredictable and difficult undertaking. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The prior art of Horn, which anticipates many of the claims, expressly teaches that specific claimed fluorophores such as fluorescein will not function. Horn states "Extensive quenching was observed with the BODIPY FL-labeled oligomer, in contrast to the fluorescein- and Texas Red-labeled oligomers which did not show an noticeable quenching under the same hybridization conditions (see column 14, lines 23-27)." Thus, Horn expressly teaches that fluorescein and rhodamine based labels do not show quenching upon hybridization.

Working Examples

The specification has several working examples (see figure 4, for instance), but the data in the specification is inconsistent. In figure 2, an internal label with fluorescein resulted in fluorescence increase upon hybridization while the 5' label resulted in

fluorescence decrease. But in figure 4, hybridization of 5' fluorescein label had comparatively minimal effect on the fluorescence.

Guidance in the Specification.

The specification provides significant guidance, as shown in the working examples, but does not resolve the issue of why the fluorescence results are inconsistent. The specification does not specifically provide any description or details which would permit the ordinary practitioner to determine which labels will function in the method. In particular, there is no teaching for how non fluorescent labels would be used, such as haptens. Also, there is no teaching or guidance with respect to which parameters consistently evoke increased fluorescence and which parameters are associated with quenching upon hybridization and which parameters result in no effect upon hybridization. Without specific guidance on the issue of how to design an oligonucleotide that will show a change upon hybridization, the specification fails to enable the full scope of the claimed invention.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the prior art specifically states that fluorescein is not quenched and will not function while there is a working example in which fluorescein shows both quenching and increased fluorescence depending upon the label location. Given this express conflict between the specification and the prior art, and failure of the specification to provide guidance on how to resolve this conflict,

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and given the broad scope of the claims in the unpredictable art of biochemistry, it is concluded that undue experimentation would be required to make and use the invention as claimed.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman  
Primary Examiner  
Art Unit 1637

9/10/05